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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,286	10/20/2006	Jose Vicente Castell Ripoll	020884-000009	8850

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,286	RIPOLL ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0710*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 11, 13-20 are pending in the application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/27/2010 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gomez-Lechon et al (IDS), in view of Bort et al (IDS) and Brimer (IDS).

Gomez-Lechon et al. teach that in vitro metabolism models can speed up the identification of new drug candidates, and pharmaceutical companies are increasingly making use of such model. Gomez-Lechon et al. discuss advantages and limitation of currently existing in vitro models including liver microsomes, human heptocytes and CYP engineered cells (see Table 1). Gomez-Lechon et al. teach that using human hepatocytes for this application has limitations such as losing expression of many hepatic proteins including CYPs during culture (see page 297, 1st col., 2nd paragraph). Gomez-Lechon et al. also teach that using hepatic cell lines expressing single CYP has limitations including lack of phase II enzymes, uncoupled metabolic pathways, no physiological levels of enzymes, impossibility of induction studies and no in vitro/in vivo correlations (see Table 1). Moreover, in cDNA-expressing systems a single CYP interacts with an electron-carrier/supplier protein, while in liver hepatocytes many CYPs can interact with them, thus lead to incorrect predictions of the relative distributions of individual CYPs to the metabolism of a drug (see page 299, 1st col., last paragraph). Gomez-Lechon et al. further indicate that the future improvements for those CYP engineered cells to serve as in vitro model includes co-expression of several CYPs, expression of phase II enzymes and development of cells responsive to induction (see Table 1). Gomez-Lechon et al. state that there is a need for hepatic cell lines expressing the whole spectrum of human xenobiotic-metabolizing enzymes as an alternative to primary cultures, and the hepatic-specific expression of a given gene is accomplished by the concerted action of a number of liver-enriched and ubiquitous regulatory factors. Gomez-Lechon et al. suggest that a promising experimental approach is the use of adenoviral vectors to allow simultaneous expression of multiple genes (see page 307, bridging paragraph). Gomez-Lechon et al. teach that adenoviruses encoding two of the most relevant

liver enriched transcription vectors have been successfully generated and transduced to HepG2, a cell line of hepatic origin.

However, Gomez-Lechon et al. do not teach actual practice of the suggested approach of transfecting multiple adenoviral vector that expresses different phase I or phase II enzyme to cells of hepatic origin.

Bort et al. teach a method of studying hepatic metabolism of diclofenac using liver epithelial cell lines that transfected with specific CYP genes (see page 792, last paragraph through page 793, 1st col.). Bort et al. teach that comparison of metabolism of diclofenac in both primary hepatocytes and said genetically engineered cell lines is able to identify CYP that are required for said drug metabolism (see page 793, last paragraph and Figure 7).

Brimer et al. teach a cellular model, Caco-2 cells, which is polarize in culture and expresses Pgp, and retain functional characteristics of human small intestine, to be transfected with vectors expressing CYP3A4 and p450 reductase and/or Pgp. Brimer et al. teach that Caco-2 cells express CYP3A4 only weakly without exogenous expression (see page 803, 2nd col., 3rd paragraph). Brimer et al. teach upon transfection with the adenoviral vector encoding CYP3A4, a dose dependent increase in protein expression was observed (see Figure 2A and legend). Brimer et al. further teach that this model can be used to study interactions between drug metabolic enzymes and drug transporter, including other phase I and phase II enzymes with drug transporters (see page 809, 2nd col., last paragraph).

It would have been obvious an ordinary skill in the art to introduce adenoviral expression vectors that expresses different Phase I or Phase II enzymes to cells of hepatic origin to build an in vitro model for studying drug metabolism based on the teaching of Gomez-Lechon et al. The

teaching of Gomez-Lechon et al. clearly established that there is a need for such engineered cell line to be made for the purpose of studying drug metabolism. Bort et al. has demonstrated that this approach is feasible using hepatic cell lines transfected vector expressing single CYP enzymes and assessing hepatic metabolism of diclofenac. Since Gomez-Lechon et al. taught the limitation of cell line expressing single CYP, an ordinary skilled in the art would have been motivated to modify such system by introducing additional Phase I or Phase II enzymes such that the cell line will reflect the whole spectrum of human xenobiotic metabolizing enzyme expression profile. Moreover, Brimer et al. has demonstrated that it is feasible to introduce adenoviral vector encoding CYP3A4 into Caco cells and achieve certain level of expression by control the amount of vector which are introduced. Moreover, Brimer et al. demonstrated that introducing multiple enzymes that affects the drug metabolism is feasible, and useful in studying interactions between said enzymes. The level of skill in the art is high as evidenced by transducing hepatic cell lines using adenoviral vectors have been proven successful, and the identification of cDNA encoding Phase I and Phase II enzymes wherein such information is available to the public. The ordinary artisan having the knowledge of cDNA encoding of Phase I and Phase II enzymes would have reasonable expectation of success to generate adenoviral vectors expressing sense or anti-sense drug metabolizing enzymes to up or down-regulating specific enzymes in a cell of hepatic origin to best mimic the hepatocytes in vivo. Once such in vitro model is made, it would have been obvious to the ordinary artisan to use such model to study metabolism, pharmacokinetics, potential idiosyncratic heptotoxicity and or potential medicament interaction of a drug as claimed. The claimed cells expressing different phase I or phase II enzymes and the method of making them by transfecting cells with adenoviral

expression vectors would have been obvious because a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, in the instant case, as suggested by Gomez-Lechon et al., to make the claimed cell model. As stated above, the ordinary artisan having the knowledge of cDNA encoding of Phase I and Phase II enzymes would have reasonable expectation of success to generate adenoviral vectors expressing sense or anti-sense drug metabolizing enzymes to up or down-regulating specific enzymes in a cell of hepatic origin. Therefore, the claimed invention is not of innovation but of ordinary skill and common sense, and would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Response to Arguments

In response to this rejection, Applicants argue that Gomez-Lechon and Bort, alone or in combination, do not teach conferring on transformed cells specific phenotypic profiles. Applicants argue that the transformed cells of Gomez-Lechon use adenoviral vectors encoding transcription factor can be responsible for the transcriptional activation of several genes. Applicants assert that if one of skill in the art started with the Gomez-Lechon cells with the adenoviruses encoding transcription factors, it would be impossible to confer specific phenotypic profiles on transformed cells because a variety of CYP genes could be increased in an unknown manner. Applicants further assert that Bort does not remedy the deficiency because it does not teach expressing multiple genes. Applicants point to the disclosure of the Ripoll Declaration to demonstrate the claimed method is able to confer specific phenotypic profiles on transformed cells compared to the imprecise control of expression of CYP genes through the use of transcription factors as discussed in Gomez-Lechon. Applicants assert that part one of the

Declaration showed the transduction of HepG2 cells using increasing amounts of adenoviral vectors encoding different CYP proteins, and the result demonstrated that the amount of metabolites generated from each of the enzymes increased linearly as a function of MOI of the adenoviruses used for transduction. Applicants assert that the claimed method allows individual control of the enzymatic activity of the biotransformation enzymes. Applicants assert that the increase in enzymes by transcription factors as used in Gomez-Lechon results in unknown, and the specific phenotypic profile is not possible. Applicants further indicate that in part two of the Declaration, the transformed cells of the instant application are able to approximate human hepatocytes whereas the cells of Gomez-Lechon are not. Applicants state that the cells of Gomez-Lechon are not suitable for instant application and would not lead to "specific phenotypic profiles." Moreover, Applicants argue that there are many different methods of increasing expression of CYP enzymes in hematoma cells, not a finite number of predictable solutions. Applicants listed 5 possible solutions to increase expression of CYP from Gomez-Lechon, and 1 from Bort, and concluded that none of them are appropriate for conferring on transformed cells specific phenotypic profiles. Applicants also cited Rodriguez-Antona to demonstrate that there is no correlation between mRNA level and the protein activity level. Applicants assert that the use of adenoviral vectors to control the activity of the corresponding biotransformation enzymes was unexpected over Gomez-Lechon because Gomez Lechon measured mRNA levels in the cell but not the enzyme products. Applicants assert that Bort does not teach that a given compound can be metabolized using a plurality of biotransformation enzymes. Applicants thus conclude that the claimed invention is novel and unobvious.

The above arguments have been fully considered but deemed unpersuasive. The detailed reason for obviousness has been set forth above. In response to the argument directed to lack of teaching on the "specific phenotypic profile," Applicants are reminded that the instant specification does not providing a definition for such specific phenotypic profile which set it apart from the teaching from the prior art. In fact, [0026] discloses "said model comprises a set of expression vectors that confer to the transformed cells a phenotypic profile of drug biotransformation enzymes deigned at will…" As such, even through a number of different enzymes can be activated at different level, it stills meets the limitation of a specific phenotypic profile because the phenotype of transformed cells is specific to said transformed cell, and the level of activation can be measured at mRNA level and/or protein level. The Ripoll declaration provides an example in which specific and individual control of expression of ectopic DNA sequences is achieved, and the declaration states: "specific phenotypic profiles of Phase I or Phase II drug biotransformation enzymes can be conferred on transformed cells." It is unclear which transformed cell model in Figure 1 (A-F?) is considered to be such specific phenotypic profiles because the specification does not provide describe the specific criteria for such phenotype. If Applicants wish to use one of the transformed cell model given in the example as "specific phenotypic model" the claim would have to recite the specific criteria of said phenotype so that it would distinguish the claimed method from the prior art.

Applicants' argument focuses on the difference between expressing multiple CYP and expressing transcription factors that regulates CYP as alleged taught by Gomez-Lechon. However, Gomez-Lechon's teaching is not limited to ectopic expression of multiple transcription factors. In discussing the advantages and limitations on in vitro models, Gomez-Lechon et al. in

factor teach CYP engineered cells for co-expression several CYPs, expression of phase II enzymes and development of cells responsive to induction as future improvements (see page 298, Table 1, lower right corner). Although Gomez-Lechon has not performed the experiment, it clearly set forth finite number of solutions to solve the problem. Even considering the 5 solutions listed by Applicants, the number of possible approaches is finite. In addition, if the 6 possible solutions have been tested and proved to fail, it would have been obvious to an ordinary skill in the art to use new approaches such as co-expression of several CYPs. While the teaching of Rodriguez-Antona suggested that there is no significant correlation between mRNA and protein activity for CYP2C9, CYP2A6 and CYP2E1, the majority of the CYP measured showed correlation between mRNA and enzymatic activity (CYP1A1, 1A2, 3A4, 2D6 and 2B6). Based on such teaching, one of ordinary skill in the art would in fact know which of the CYPs can be regulated at pre-translational level, and design the combination of ectopic expression accordingly. The teaching of Bort provides an example that in vitro model for CYP engineered cell lines may be used to determine which CYP is responsible for metabolize a specific drug. The teaching of Brimer et al. indicates that the level of ectopic expression of CYP2A4 can be controlled specifically by using adenoviral vector because it demonstrates that dose dependent increase in CYP3A4 protein was observed from different doses of MOI (see Figure 2). As such, the combined teaching from the prior art demonstrates that co-expressing multiple CYP in hepatic cells of human origin at controlled level is predictable. Contrary to Applicants' assertion, there is finite number of predictable solutions to ordinary skill in the art, and the ordinary skill in the art would have been motivated to at least to try co-expressing multiple CYPs because it is specifically suggested by Gomez-Lechon.

The Declaration under 37 CFR 1.132 filed 7/27/2010 is insufficient to overcome the rejection of claims 1-9, 11, 13-20 based upon 35 U.S.C as set forth in the last Office action.

The Declaration has been fully considered. The Declaration states that the claimed method provides specific and individual control of expression of ectopic DNA sequences so that specific phenotypic profiles of Phase I or Phase II drug biotransformation enzymes can be conferred on transformed cells, and the method is able to reproduce in vitro the metabolic idiosyncrasy of humans with better results than the imprecise method discussed in Gomez-Lechon. The Declaration further assert that the enzymatic activities obtained are comparable with that found in human hepatocytes cultures, whereas the enzymatic activity provided in Gomez-Lechon is much lower than that found in human hepatocyte culture. As discussed above, since specific phenotypic profiles is not defined by the instant specification, the phenotype of the claimed cell does not distinguish from the prior art taught phenotype. As for comparing the expression level of transforming cells with CYP3A4 and transforming cells with transcription factors as taught by Gomez-Lechon, it is off the point because the rejection is not based on solely on the teaching of expressing transcription factors, but rather, the combination of Gomez-Lechon, Bort and Brimer as discussed above. In response to applicant's argument that the claimed cells have higher level of expression than that of prior art cells, it is noted that the features upon which applicant relies (i.e., the high expression of specific CYP) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, for reason discussed in previous office action and above, this rejection is maintained.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636